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The diagnostic utility of the Heston index in gated SPECT to detect multi-vessel coronary artery disease

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Summary
Objectives: Although the Heston index, derived left ventricular (LV) volumetric analysis, is reported to best represent transient LV dilation on non-gated single-photon emission computed tomography (SPECT), its diagnostic performance has not been proven to identify extensive coronary artery disease (CAD) as assessed by coronary angiogram. Accordingly, we sought to evaluate the diagnostic utility of Heston index to detect multi-vessel CAD.
Methods: Post-stress and resting electrocardiogram-gated ^{99m}Tc-sestamibi SPECT was performed in 223 patients with suspected or known CAD. All of the patients underwent coronary angiography within 3 months of gated SPECT. The summed stress, summed rest, and summed difference scores were calculated using a 20-segment model. The left ventricular end-diastolic volume (EDV), end-systolic volume (ESV), and ejection fraction (EF) were calculated automatically with the QGS program. In addition, stress-to-rest ratios of EDV, ESV, and (ESV $\times$ 5 + EDV) were calculated; the latter was defined as Heston index.
Results: In the 104 patients with multi-vessel CAD, the summed stress score (17.5 ± 10.0 vs. 11.7 ± 9.2, $p < 0.001$), the summed difference score (9.1 ± 6.3 vs. 4.3 ± 4.2, $p < 0.0001$), the Heston index (1.17 ± 0.15 vs. 1.02 ± 0.13, $p < 0.0001$), the stress-to-rest ratio of EDV (1.05 ± 0.10 vs. 0.99 ± 0.09; $p < 0.0001$), and that of ESV (1.23 ± 0.21 vs. 1.04 ± 0.17; $p < 0.0001$, respectively) were greater than in the 119 patients with one-vessel CAD or insignificant lesion. The best cut-off value was determined as 1.09 for Heston index, giving a sensitivity of 76%, specificity of 77% for detection of multi-vessel CAD. Multiple stepwise logistic regression analysis

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showed that Heston index ≥1.09, summed stress score ≥14, and summed difference score ≥9 were the independent predictors of detecting multi-vessel CAD, yielding a sensitivity of 76% and specificity of 77% (global χ^2, 88.8).
Conclusions: The Heston index is simple and achieves higher diagnostic value in the detection of multi-vessel CAD, compared with conventional analysis alone.

Introduction

Transient ischemic dilation of the left ventricle (LV) has been established as a powerful diagnostic finding of stress myocardial perfusion imaging, and is usually regarded as a marker of severe and extensive coronary artery disease (CAD) [1—6]. However, problems regarding transient ischemic dilation are its lack of universally accepted quantitative methods or computer software. Different methods with different cut-off points defining an increase in the LV size at stress in comparison to rest images were applied in previous studies [3,6—8]. To overcome this shortcoming, Heston and Sigg have proposed an index defined as a stress-to-rest ratio of {(end-systolic volume) × 5 + end-diastolic volume; ESV × 5 + EDV} as a marker for severe and extensive CAD [9], though this unique index has not been evaluated for its diagnostic performance in patients who underwent coronary angiogram. The objectives of this study, therefore, were to examine the diagnostic utility of the Heston index in patients with suspected or known CAD, in comparison to conventional myocardial perfusion indexes.

Methods

Study patients

We retrospectively evaluated 223 consecutive patients with known or suspected CAD, who underwent both stress myocardial perfusion imaging and coronary angiography. Clinical grounds for suspected or unknown CAD were based on clinical symptoms, coronary risk profiles, electrocardiographic findings, or past medical history. They were aged 64 ± 10 years; 184 were men and 39 women. No patient with acute myocardial infarction, unstable angina, or those with history of coronary bypass grafting was included. Written informed consents were obtained from all of the patients.

Coronary risk factors included in the assessment were hypertension, hypercholesterolemia, diabetes mellitus, and cigarette smoking. Hypertension was defined as a history of systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg or documented hypertension on at least two occasions in outpatient clinics. Hypercholesterolemia was defined as fasting serum total cholesterol of ≥220 mg/dl [10]. Diabetes mellitus was diagnosed using a criteria proposed by the Japanese Diabetic Society [11].

Stress myocardial perfusion imaging

To successfully obtain adequate electrocardiogram-gated single-photon emission computed tomography (SPECT), patients with atrial fibrillation or frequent extrasystoles were excluded. In addition, patients in whom automatically derived LV volumes could not be measured due to severe perfusion defects were excluded.

In 151 patients, exercise myocardial perfusion imaging with ^{99m}Tc-sestamibi was performed using the 1-day protocol [12]. Symptom-limited multi-step exercise using a bicycle ergometer was performed [13]. ^{99m}Tc-sestamibi (259 MBq) was administered when submaximal heart rate, chest pain, ST-segment depression of ≥0.1 mV, or leg fatigue developed. Then, exercise was continued for 1 min at the same level as before. In the remaining 72 patients, adenosine triphosphate disodium (0.16 mg/kg min) was administered intravenously for 6 min [14], and 3 min later, ^{99m}Tc-sestamibi (259 MBq) was given intravenously. In both protocol, electrocardiogram-gated SPECT was acquired 30 min after the stress [15]. Four hours later, the patients were given ^{99m}Tc-sestamibi (777 MBq) while at rest. Thirty minutes later, electrocardiogram-gated SPECT image acquisition was started.

Data were acquired with a three-detector gamma camera (Prism 3000XP, Picker, Cleveland, Ohio, USA) for 360-degree arcs (in 6-degree-wide directions, taking 30 s/direction for 20 times). A low-energy high-resolution parallel multi-hole collimator was used. The maximum matrix size was 64 × 64. When taking electrocardiogram-gated images, the R—R interval was divided by the R wave trigger into eight equal portions. End-diastolic and end-systolic myocardial perfusion images were thus obtained. All the patients were

Table 1 Calculation of stress-to-rest volume ratios

Heston index $= \frac{\text{Stress (ESV}\times 5+\text{EDV)}}{\text{Rest (ESV}\times 5+\text{EDV)}}$
Stress-to-rest ratio of EDV $= \frac{\text{Stress EDV}}{\text{Rest EDV}}$
Stress-to-rest ratio of ESV $= \frac{\text{Stress ESV}}{\text{Rest ESV}}$

EDV: end-diastolic volume, ESV: end-systolic volume.

in sinus rhythm during the image acquisition. SPECT images were reconstructed from the data with a data processor (Odyssey VP, Picker, Cleveland, Ohio, USA) combined with a Butterworth filter (order 8; cut-off frequency 0.25) and a ramp filter [14].

According to a method reported elsewhere, each SPECT image was divided into 20 segments [14,16]. The accumulation of radioisotope in the myocardium was visually evaluated by two cardiologists, who were blinded to clinical data, with the use of a 5-grade scale: 0 (normal), 1 (slight reduction of uptake), 2 (moderate reduction of uptake), 3 (severe reduction of uptake), or 4 (absent of radioactive uptake). The total of the scores for all the segments during exercise and at rest was designated the summed stress scores and the summed rest scores, respectively. Summed stress score minus summed rest score was defined as the summed difference score [17]. Disagreements in image interpretation were resolved by consensus.

Each reconstructed short-axis electrocardiogram-gated SPECT image was processed by the QGS program developed by Germano et al. [18], to automatically calculate the LV end-diastolic volume (EDV), LV end-systolic volume (ESV), and LV ejection fraction (EF). In addition, stress-to-rest ratios of EDV, ESV, and (ESV $\times$ 5 + EDV) were calculated; the latter was defined as Heston index (Table 1) [9].

Coronary angiography

For all the patients, multi-directional coronary angiography was performed within 3 months of SPECT study, using a Judkins' method. According to the American Heart Association criteria [19], the degree of coronary artery stenosis was visually rated by 2 experienced interventional cardiologists. The criterion for clinically significant one-, two-, or three-vessel CAD was either $\geq$75% diameter narrowing of the right or left anterior descending or left circumflex coronary artery, irrespective of each coronary artery dominancy [20]. The proximal locations of each three major coronary arteries were defined by the American Heart Association criteria.

Statistical analysis

Results are expressed as mean $\pm$ 1 S.D. Student's t test was used to compare the means of the continuous variables, and contingency tables were analyzed using a χ^2 test. To determine cut-off values of volumetric and functional gated SPECT parameters for multi-vessel CAD, a receiver-operating characteristic curve analysis was performed. Univariate analysis was conducted with the logistic regression method and stepwise multivariate analysis was conducted with the multiple logistic regression method. Factors that showed a p value of <0.05 in the univariate analysis were selected for multivariate analysis. Linear discriminant analysis (with stepwise variable selection with Wilks' Lambda, which is the ratio of the within-groups sum of squares to the total sum of squares) was used to assess the potential to correctly identify multi-vessel CAD. A Bayes rule with equal prior probability was used for the identification, and results are presented as sensitivity, specificity, and accuracy. A p value of <0.05 was considered significant. The statistical computations were performed using the SPSS-PC+ computer program, version 11.0 (SPSS Inc., Chicago, Illinois, USA).

Results

Clinical characteristics of the patients

Of the 223 patients, left main CAD was found in 5, three-vessel CAD in 34, two-vessel CAD in 70, one-vessel CAD in 58, and insignificant lesions in 61: multi-vessel CAD in 104 and one-vessel CAD or insignificant lesions in 119. Demographic and other variables are shown in Table 2. The prevalence of diabetes mellitus was higher in patients with multi-vessel CAD than in those without (52% vs. 34%, $p < 0.01$), whereas that of other coronary risk factors, demographic characteristics and incidence of previous myocardial infarction were similar. In addition, there was no significant difference between two groups in frequency of stress protocol used in this study.

Myocardial perfusion analysis

In patients with multi-vessel CAD, the summed stress score (17.5 ± 10.0 vs. 11.7 ± 9.2, $p < 0.001$) and summed difference score were greater (9.1 ± 6.3 vs. 4.3 ± 4.2, $p < 0.0001$) than in those with one-vessel CAD or insignificant lesions, whereas the summed rest score was similar (8.4 ± 8.9 vs. 7.5 ± 8.7, p = NS) (Table 3).

Table 2 Comparison of clinical characteristics between patients with multi-vessel CAD and those without multi-vessel CAD.

	Patients with multi-vessel CAD ($n = 104$)	Patients without multi-vessel CAD ($n = 119$)	p value
Age (years)	63 ± 10	65 ± 10	NS
Gender (men/women)	91/13	93/26	NS
Height (cm)	164 ± 7	163 ± 9	NS
Body weight (kg)	66 ± 11	65 ± 13	NS
Body mass index	24.4 ± 3.1	24.2 ± 3.3	NS
Coronary risk factors			
Hypertension	76 (73%)	90 (76%)	NS
Hypercholesterolemia	72 (69%)	80 (67%)	NS
Diabetes mellitus	54 (52%)	41 (34%)	<0.01
Smoking	52 (50%)	63 (53%)	NS
History of myocardial infarction	43 (41%)	42 (35%)	NS
Stress protocol (ergometer/ATP)	69/35	82/37	NS

ATP: adenosine triphosphate disodium, CAD: coronary artery disease.

LV functional analysis including Heston index

There were no significant differences between the two groups in the baseline cardiac function, such as EDV, ESV, and EF at rest. Comparing indexes of cardiac function during stress, EF was significantly lower in patients with multi-vessel CAD than in those with one-vessel CAD or insignificant lesions, while EDV and ESV were similar (Table 3). In patients with multi-vessel CAD, Heston index was greater (1.17 ± 0.15 vs. 1.02 ± 0.13, $p < 0.0001$) than in patients with one-vessel CAD or insignificant lesion. The stress-to-rest ratios of EDV and ESV were also greater in patients with multi-vessel CAD than in those with one-vessel CAD or insignificant lesions (Table 3).

Detection of multi-vessel CAD

In detecting multi-vessel CAD by use of myocardial perfusion analysis, previously reported cut-off points for severe CAD were applied: summed stress score ≥14 and summed difference score ≥9 [3,17].

Table 3 Comparison of scintigraphic findings between patients with multi-vessel CAD and those without multi-vessel CAD

	Patients with multi-vessel CAD ($n = 104$)	Patients without multi-vessel CAD ($n = 119$)	p value
Myocardial perfusion			
Summed stress score	17.5 ± 10.0	11.7 ± 9.2	<0.001
Summed rest score	8.4 ± 8.9	7.5 ± 8.7	NS
Summed difference score	9.1 ± 6.3	4.3 ± 4.2	<0.0001
LV function at rest			
EDV (ml)	105 ± 36	103 ± 50	NS
ESV (ml)	49 ± 30	50 ± 42	NS
EF (%)	56 ± 11	57 ± 13	NS
LV function at stress			
EDV (ml)	110 ± 37	102 ± 50	NS
ESV (ml)	57 ± 31	51 ± 42	NS
EF (%)	50 ± 10	55 ± 13	<0.01
Indexes			
Heston index	1.17 ± 0.15	1.02 ± 0.13	<0.0001
Stress-to-rest ratio of EDV	1.05 ± 0.10	0.99 ± 0.09	<0.0001
Stress-to-rest ratio of ESV	1.23 ± 0.21	1.04 ± 0.17	<0.0001

CAD: coronary artery disease, EDV: end-diastolic volume, ESV: end-systolic volume, EF: ejection fraction, LV: left ventricular.

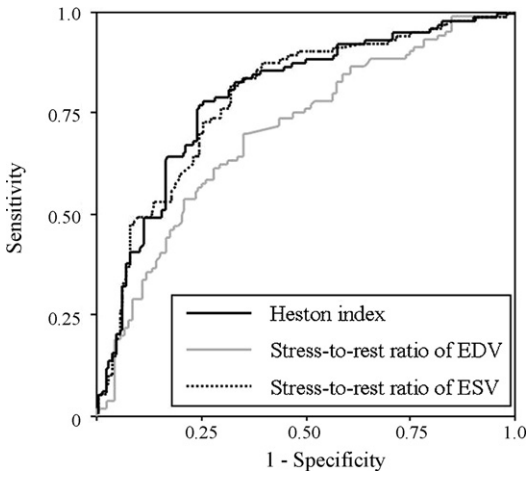

Figure 1 Receiver-operating characteristic curves to discriminate between patients with multi-vessel coronary artery disease and those without it. Heston index and stress-to-rest ratio of end-systolic volume (ESV) yielded higher sensitivity and specificity than stress-to-rest ratio of end-diastolic volume (EDV). The area under the curve was 0.796 for Heston index, 0.792 for stress-to-rest ratio of ESV, and 0.704 for stress-to-rest ratio of EDV.

The sensitivity, specificity, and accuracy in the detection of multi-vessel CAD were 61%, 69%, and 65%, respectively, with a summed stress score ≥14, and 45%, 87%, and 68%, respectively, with a summed difference score ≥9. The receiver-operating characteristic curves were used to identify the best cut-off value of Heston index, stress-to-rest ratio of EDV and ESV for detection of multi-vessel CAD (Fig. 1). The area under the curve was 0.796 (95% confidence interval (CI), 0.737—0.856) for Heston index, 0.704 (95% CI, 0.636—0.772) for stress-to-rest ratio of EDV, and 0.792 (95% CI, 0.732—0.852) for stress-to-rest ratio of ESV. The cut-off value was determined as 1.09 for Heston index, giving a sensitivity of 76%, specificity of 77%, and accuracy of 76%. The cut-off value was determined as 1.01 for stress-to-rest ratio of EDV and 1.13 for stress-to-rest ratio of ESV, giving a sensitivity of 68% and specificity of 65% for stress-to-rest ratio of EDV, and a sensitivity of 73% and specificity of 73% for stress-to-rest ratio of ESV.

Univariate and multivariate analyses for the detection of multi-vessel CAD

In the univariate analysis, six parameters such as diabetes mellitus, summed stress score ≥14, summed difference score ≥9, Heston index ≥1.09, stress-to-rest ratio of EDV ≥1.01, and stress-to-rest ratio of ESV ≥1.13 were significant predictors of detecting multi-vessel CAD (Table 4). Multiple stepwise logistic regression analysis of all significant univariate parameters showed that Heston index ≥1.09, summed stress score ≥14, and summed difference score ≥9 were the strongest independent predictors of detecting multi-vessel CAD (Table 4).

The stepwise discriminant analysis was also performed in detecting multi-vessel CAD, by use of three variables related to clinical characteristics and myocardial perfusion analysis: diabetes mellitus, summed stress score, and summed difference score. The analysis showed that the combination of summed stress score and summed difference score was associated with multi-vessel CAD with a sensitivity of 45% and specificity of 87% (global χ^2, 35.4) (Figs. 2 and 3). The multivariate analysis was repeated by use of clinical, perfusion, and functional variables. This revealed that the combination of Heston index ≥1.09, summed stress score ≥14, and summed difference score ≥9 best identified multi-vessel CAD, with a higher sensitivity of 76% and specificity of 77% (global χ^2, 88.8), as compared with the combination of perfusion variables (Figs. 2 and 3).

Table 4 Univariate and multivariate analysis for detecting multi-vessel CAD

	Univariate		Multivariate	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Hypercholesterolemia	1.1 (0.6—1.9)	0.749		
Diabetes mellitus	2.1 (1.2—3.5)	<0.01		
Smoking	0.9 (0.5—1.5)	0.661		
History of myocardial infarction	1.3 (0.8—2.2)	0.354		
Heston index ≥1.09	10.3 (5.5—19.0)	<0.0001	8.8 (4.6—16.9)	<0.0001
Stress-to-rest ratio of EDV ≥1.01	3.9 (2.3—6.9)	<0.0001		
Stress-to-rest ratio of ESV ≥1.13	7.4 (4.1—13.4)	<0.0001		
Summed stress score ≥14	3.4 (2.0—5.9)	<0.0001	2.4 (1.1—4.9)	0.020
Summed difference score ≥9	5.7 (2.9—11.1)	<0.0001	2.3 (1.0—5.4)	0.050

CAD: coronary artery disease, CI: confidence interval, OR: odds ratio.

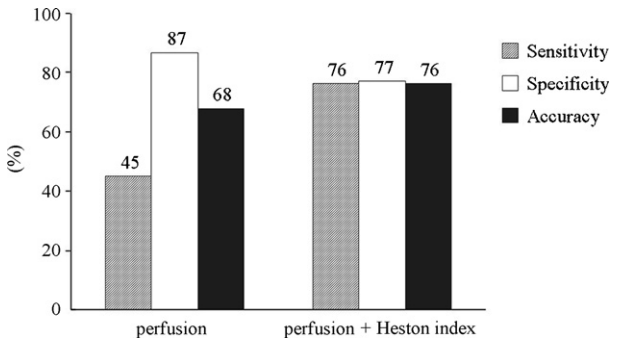

Figure 2 Diagnostic value of perfusion analysis and combination of perfusion and functional analysis in detection of multi-vessel coronary artery disease.

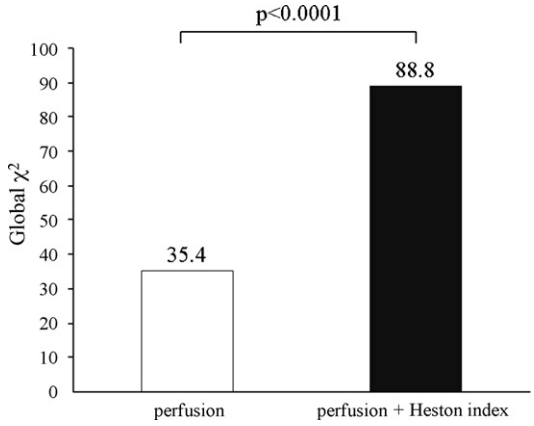

Figure 3 Incremental diagnostic value of addition of Heston index ≥ 1.09 to perfusion analysis for detecting multi-vessel coronary artery disease.

Discussion

Heston and Sigg have reported that the stress-to-rest ratio of combined EDV and ESV in gated SPECT resembled transient ischemic dilation on non-gated image [9]. Based on their mathematical model, a stress-to-rest ratio of (ESV $\times$ 5 + EDV) best represented transient LV dilation on non-gated SPECT [9]. Considering wide availability and reproducibility of gated SPECT today, clinical application of this index is promising. However, the Heston index, a stress-to-rest ratio of (ESV $\times$ 5 + EDV), has not been proven to identify severe and extensive CAD as assessed by coronary angiogram.

The present study demonstrated that the Heston index on gated SPECT significantly contributed in the detection of angiographically proven multi-vessel disease, a high-risk subset of CAD. A stress-to-rest ratio of EDV $\geq$1.01, stress-to-rest-ratio of ESV $\geq$1.13, and the Heston index $\geq$1.09 showed high specificity of 65—77% in detecting multi-vessel CAD. Among these parameters derived from the LV volumetric analysis, the Heston index was the best marker by the multivariate analysis. The extensive and severe perfusion abnormalities as represented by summed scores are well-established scintigraphic markers for multi-vessel CAD [5,21]. In the current study, a summed stress score $\geq$14 and a summed difference score $\geq$9 were also significantly associated with multi-vessel CAD, which is consistent with previous studies [3,17]. However, the addition of the Heston index on these established myocardial perfusion parameters improved the diagnostic value considerably in our study (global χ^2, 88.8 vs. 35.4). Indeed, the Heston index was characterized by a higher sensitivity of 76% as compared with summed scores showing sensitivities of 45—61%, though specificity remained similar: 77% vs. 69—87%. Myocardial perfusion imaging is often unsuccessful to detect multi-vessel CAD because scintigraphic interpretation relies on spatially relative perfusion defect analysis [7,22]. Thus, rather uniform global hypoperfusion, due to balanced reduction of blood flow, may decrease summed scores and ultimately underestimate the possibility of multi-vessel CAD with decreased sensitivity [23]. In contrast to myocardial perfusion image, the LV volumetric analysis including a stress-to-rest ratio of combined EDV and ESV in gated SPECT is independent of the shortcomings in relative perfusion defect analysis and reveals absolute value of LV volume and its changes with stress. Furthermore, sustained LV functional abnormalities after stress usually develop in patients with extensive CAD, and several markers such as a decrease in EF and an increase in ESV or a stress-to-rest ratio were reported in the detection of this high-risk subset [5,8,21,24,25]. Thus, to improve the detection of multi-vessel CAD, the addition of the LV volume and function analysis including the Heston index on the conventional perfusion analysis seems considerably important [24].

A significant weighing on ESV, rather than EDV, is the key to the Heston index. One might expect that non-gated measurements of transient ischemic dilation are weighed on average more toward EDV than ESV because the cardiac cycle spends a greater proportion of time in diastole during SPECT data acquisition. However, the change in ESV had the most strong correlation with the extent and severity of perfusion abnormalities, and the change in the stress-to-rest ratio of ESV was greater than the ratio of EDV in their study [8,25]. The importance of the ESV changes in detecting of multi-vessel CAD was also reported in previous studies [25]. These observations may be consistent with underlying mechanisms for transient ischemic dilatation, in which subendocardial hypoperfusion and systolic

LV dysfunction are more predominant etiology than actual LV dilation in end diastole [5]. Although the primary purpose of the present study was to evaluate the diagnostic value of the Heston index in the detection of angiographically documented multi-vessel CAD, the direct comparison between this index and transient ischemic dilation on non-gated image will give further insight into this important physiologic findings in patients with extensive CAD.

Another critical issue of this study was $\geq$30 min delay in the acquisition of SPECT images after the injection of ^{99m}Tc-sestamibi. Heston and Sigg also started post-stress image acquisition 20—30 min after ^{99m}Tc-tetrofosmin injection [9]. Although ischemia-related wall motion abnormalities usually disappear rapidly once myocardial ischemia is eliminated [26], there are a few cases in which wall motion abnormalities remain, even 15—30 min after elimination of ischemia; myocardial stunning being the apparent mechanism in such cases [27,28]. Therefore, the study of Heston and Sigg [9] and ours enhanced the assessment of postischemic stunning and resulted in better detection of multi-vessel CAD, because earlier initiation of image acquisition soon after the cessation of exercise may detect ischemia-related LV dysfunction which may be observed even in single-vessel CAD.

Study limitations

In the present study, different stress protocols were used: exercise and pharmacologic loading with ATP. It is well known that pharmacologic stress using coronary vasodilators resulted in predominantly intramyocardial blood flow maldistribution [29,30], with rare occasion of myocardial ischemia through blood steal phenomenon. By contrast, myocardial stunning developed in $\geq$10% of patients who underwent standard exercise stress, after the elimination of exercise-induced real ischemia [14]. Despite aforementioned difference in mechanisms causing post-stress abnormalities in myocardial perfusion and LV function, a previous study using the two stress protocols reported a good correlation between the extent of perfusion abnormality and the Heston index [9]. Ideally, it will be important to test the diagnostic value of the Heston index in a large patient population using a single stress protocol either with exercise or pharmacologic loading. In such occasion, the relation between the Heston index and changes in LV volumes with stress is necessary to be evaluated since changes in ESV or EF are also reported as useful markers for multi-vessel CAD [25,31].

Conclusion

The present study underscores the importance of the inclusion of the LV volume and function analysis with the Heston index into conventional myocardial perfusion imaging, since the computation of the Heston index is simple and achieves higher diagnostic value in the detection of multi-vessel CAD, compared with conventional analysis alone.

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